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Immunologic Potency Testing of a Multiclade HIV Vaccine

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Potency Workshop
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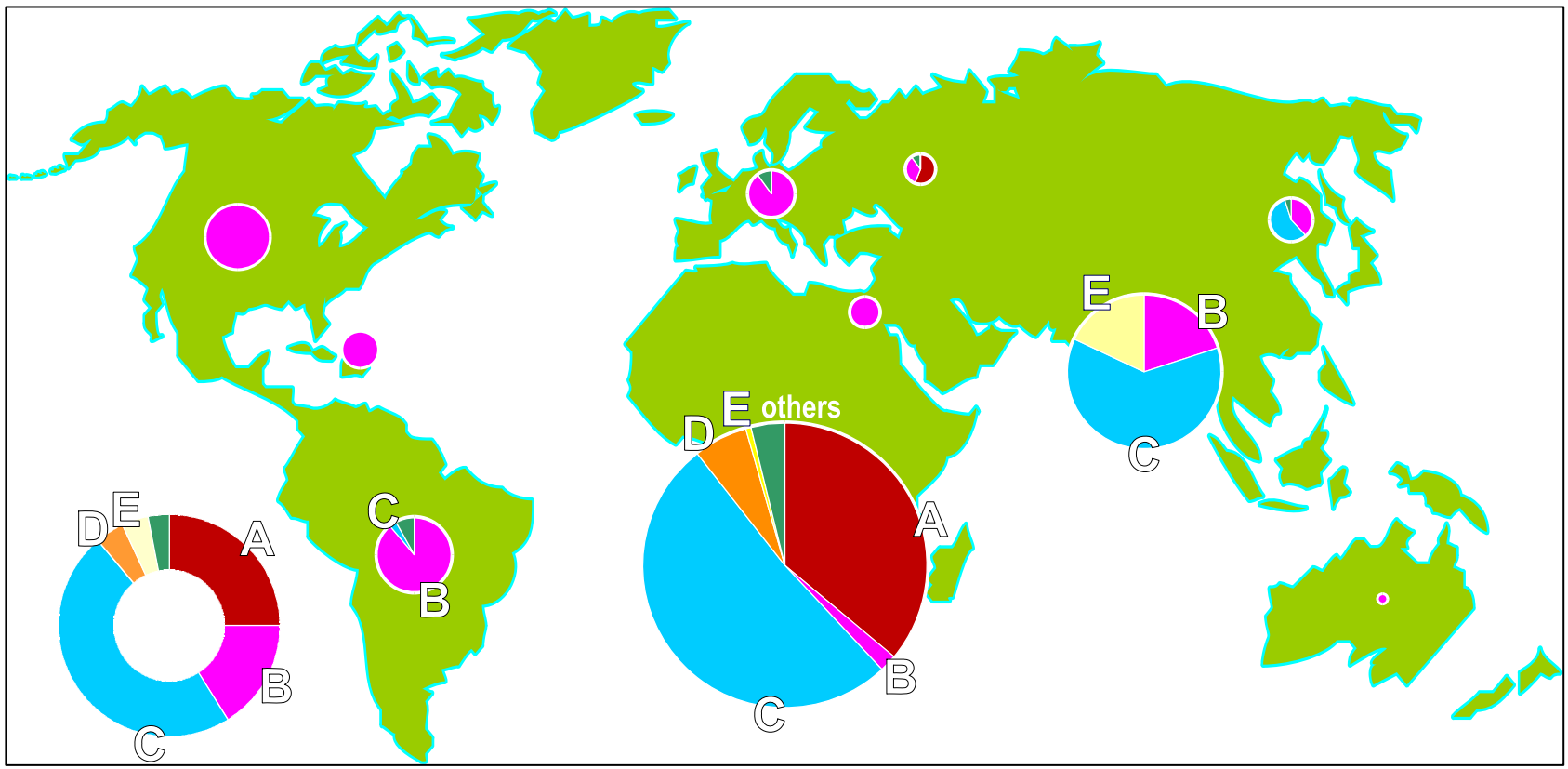
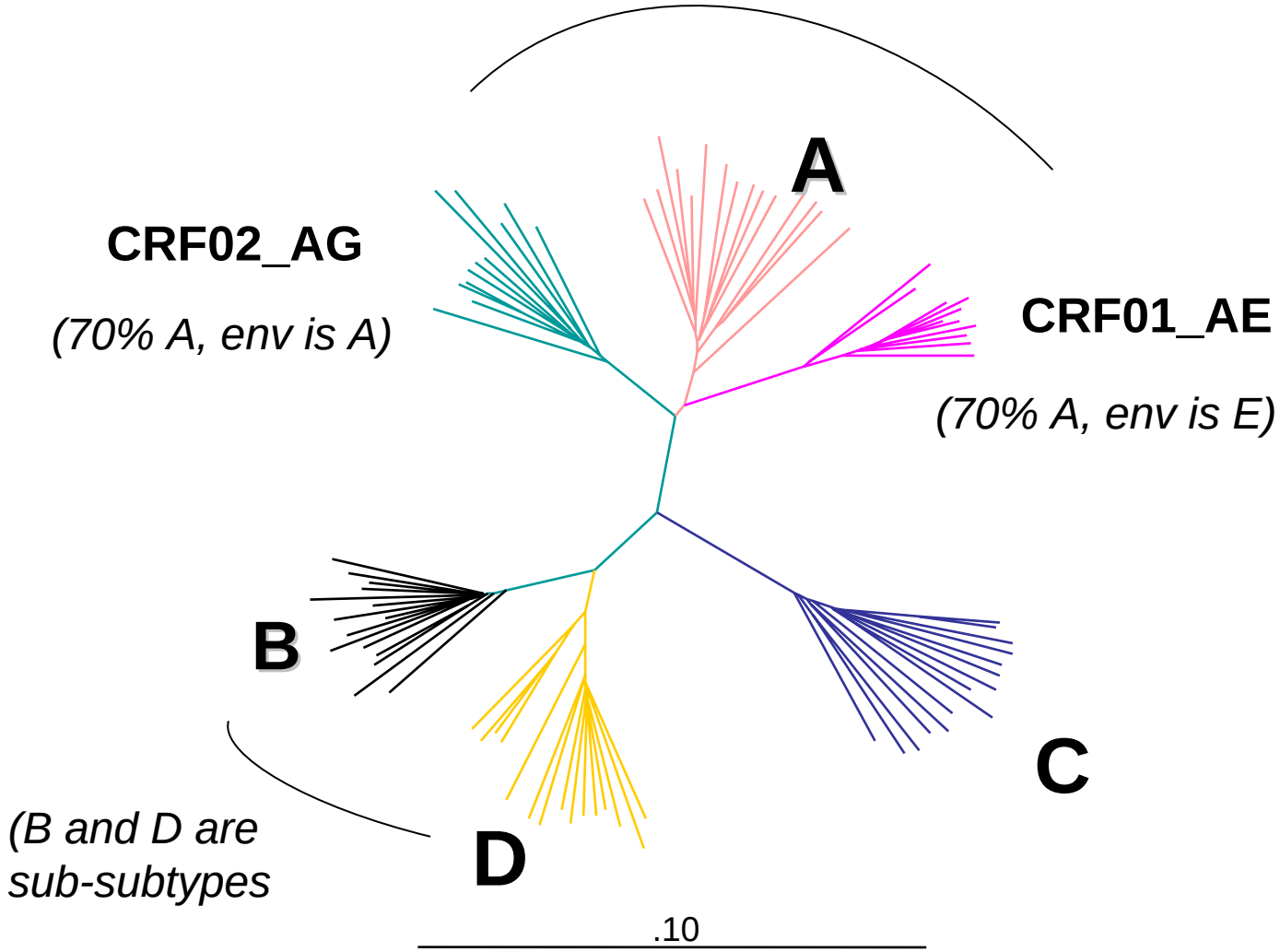
Estimated Prevalence of HIV-1 *env* Subtypes by Region, 1998



Clades are not Serotypes

- **Clades of HIV are classified based on protein sequences, not a lack of serologic cross-reactivity**
  - **Significant (though not complete) cross-reactivity in binding and neutralizing activity between clades**
- **Probably represent separate and distinct transmissions into the human population**
- **Clade differences are greatest within Env**
- **Divergence of amino acid sequences within defined antibody and T cell epitopes between clades (esp within Env) indicates that a vaccine-induced response to one clade may sub-optimally protect against challenge with another**
- **Immunization with 3 Env clades in Rhesus Monkeys gave better cross-reactive antibody and T cell responses than immunization with single Envs (without loss of response to single Env)**

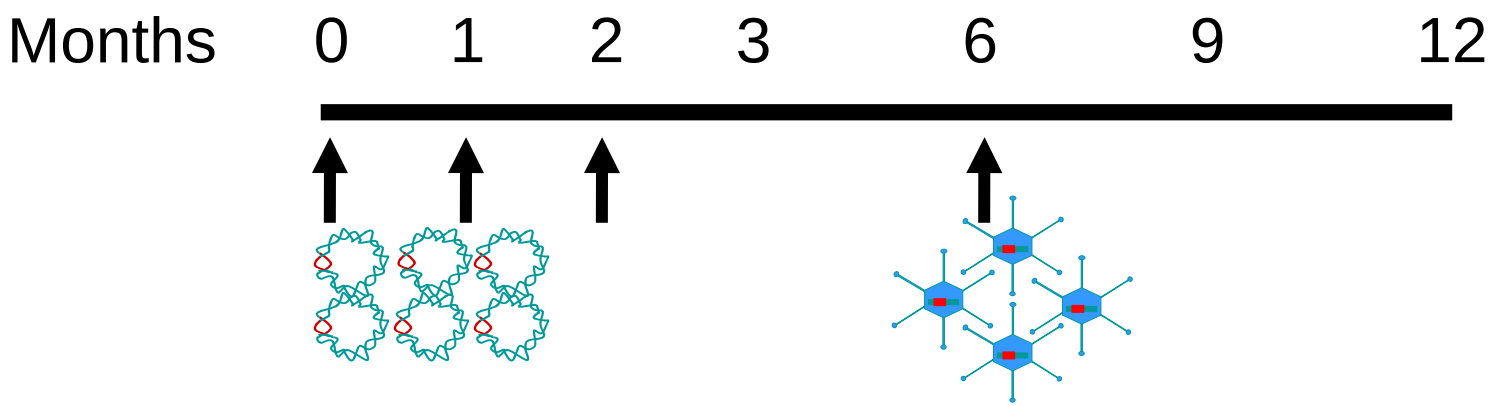
Phylogenetic Relationships of Globally Prevalent Strains



Major Assumptions Behind Initial Vaccine Research Center Vaccine Approach

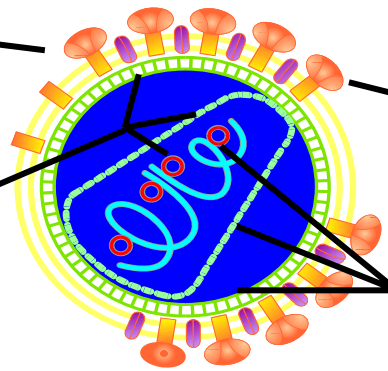
- **Vaccine-induced CD8+ CTL can control HIV infection**
  - **Delayed disease progression in an individual**
  - **Reduced spread within a population**
- **Envelope antigens are critical**
  - **Additional T-cell epitopes**
  - **Platform for NAb responses**
- **DNA priming and recombinant adenovirus boost is a potent platform for inducing CD8+ CTL**
- **Multivalency will diminish immune escape**
- **The epidemic requires a globally relevant vaccine**

VRC HIV Vaccine Development



DNA prime

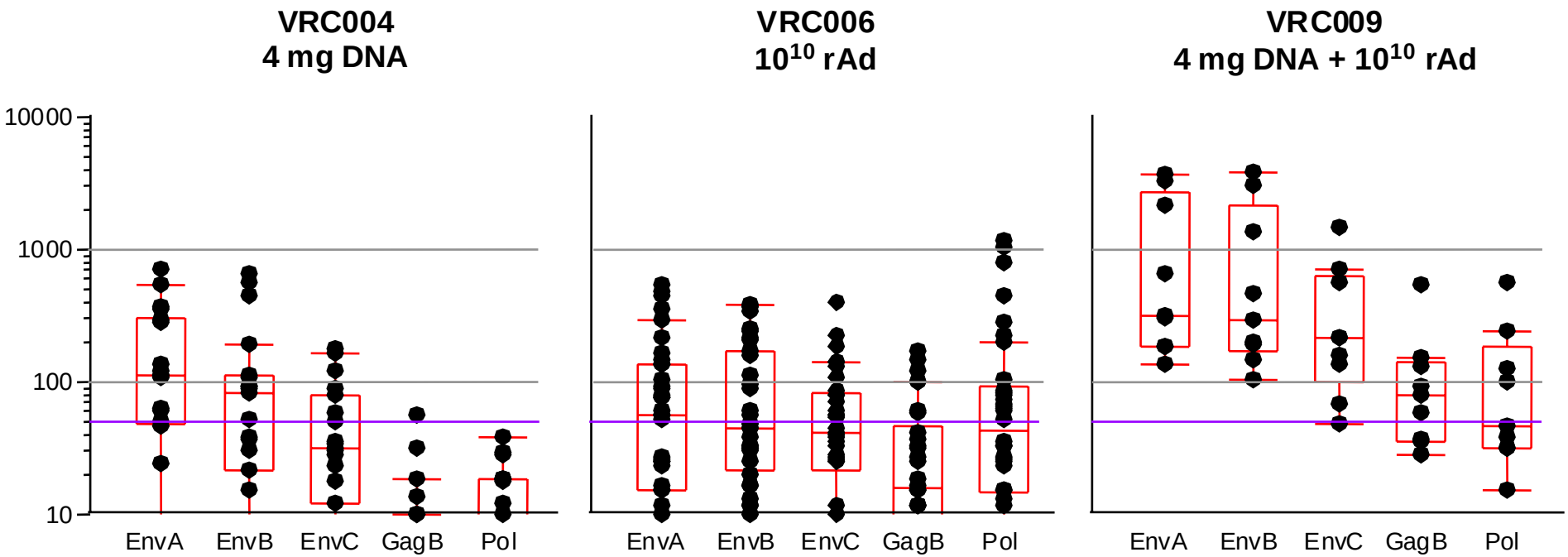
- envelope clade A
- envelope clade B
- envelope clade C
- gag clade B
- pol clade B
- nef clade B



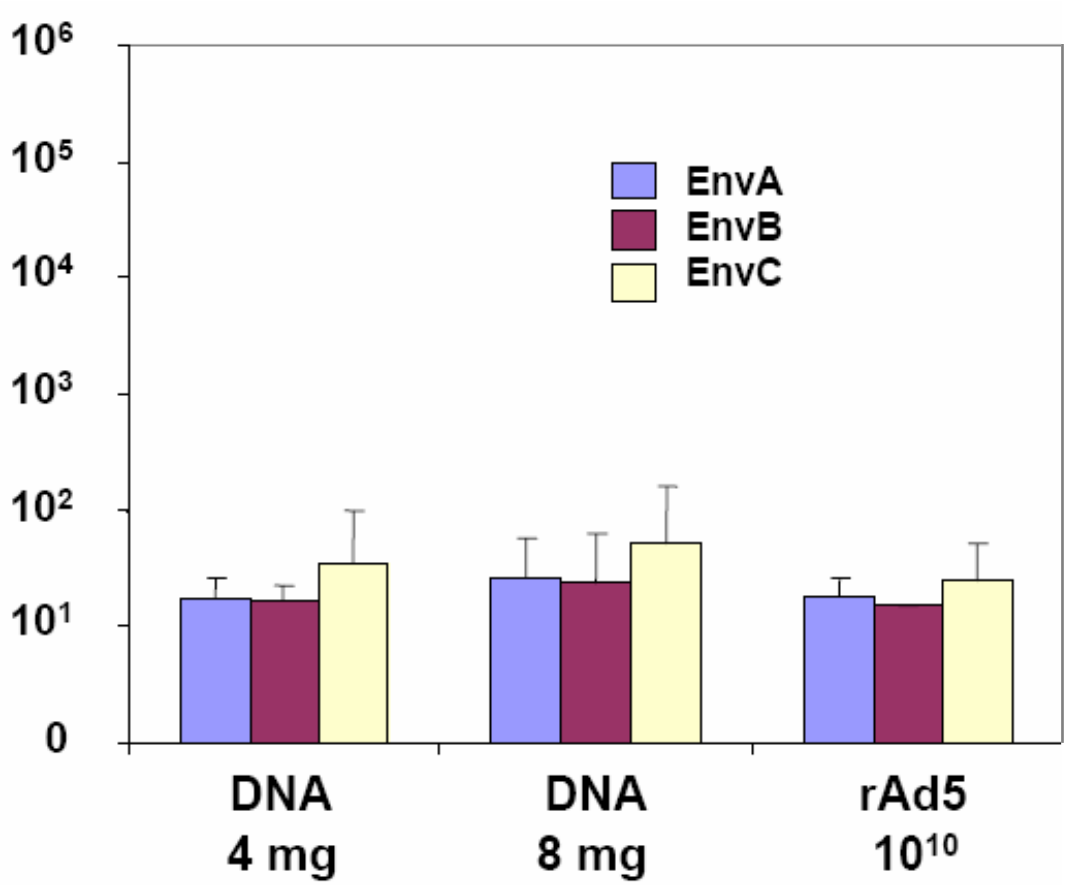
rAd5 boost

- envelope clade A
- envelope clade B
- envelope clade C
- gag/pol clade B

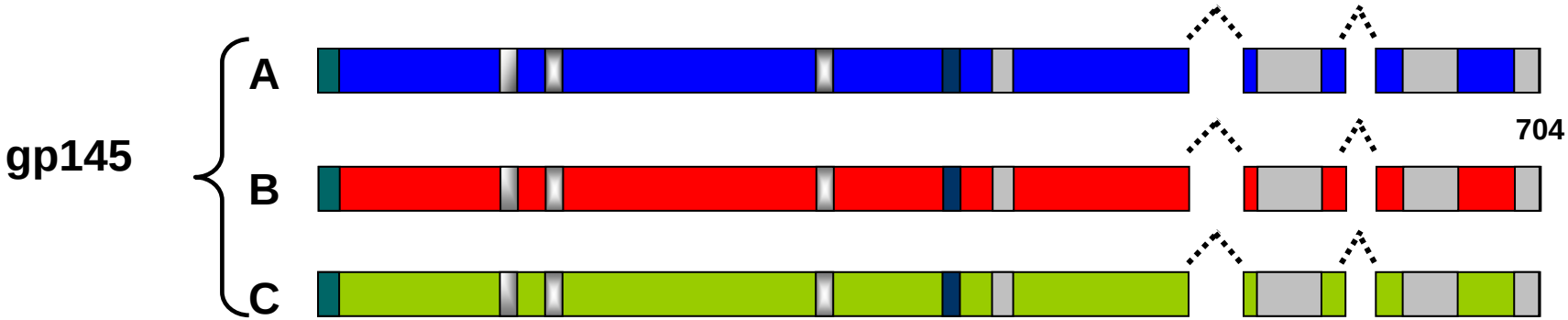
IFN-γ ELISpot Results



Antibody ELISA Results



Env Constructs and Immune Assays



- T Cell Responses: IFNγ ELISpot or combined cytokine ICS assays
- Antibody responses: ELISA and NA assays

- Overlapping peptides (15-mers by 11) for each Env construct (168 peptides each). Only 5 peptides match across all 3 clades
- Whole purified proteins

Our Goal

- **Test potency of each component of the vaccine (3 Envs, Gag, Pol, Nef) when the combined (vialed) product is administered to mice**
- **If this is not possible, test potency of each component of the vaccine (3 Envs, Gag, Pol, Nef) when each component (prior to mixing/vialing) is administered to mice**

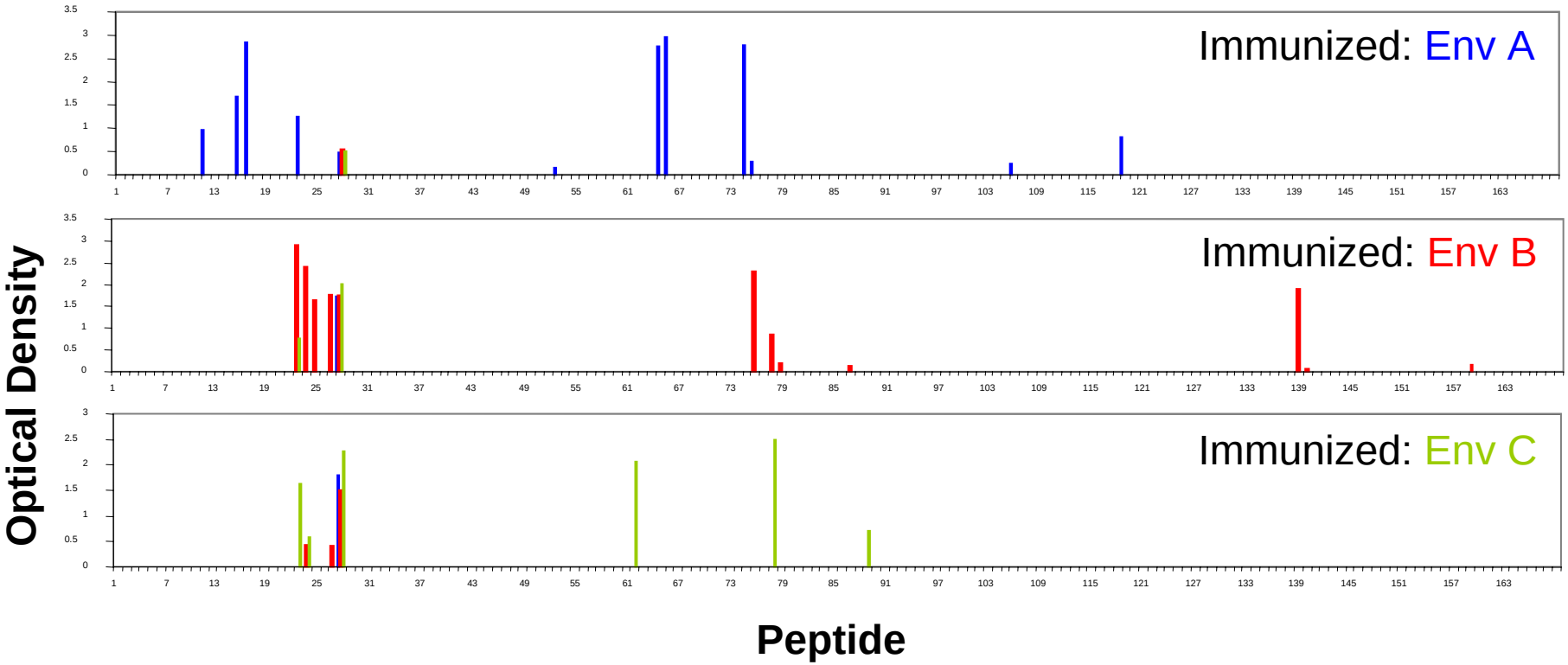
The System We Propose(d) to Use:

- **Balb/C mice**
- **Vaccinate with Env A, Env B, Env C, Gag, Pol, and Nef**
- **Test T cell and Antibody responses using overlapping peptides to each component of the combined vaccine**
- **Use immunodominant peptides to assess potency as each component of the vaccine is modulated within the mix**

Gag, Pol and Nef are not a Problem

- **Immunodominant T cell and antibody epitopes mapped**
- **In process of doing huge studies in mice to determine how changes in dose of one component of the vaccine within the 6 plasmid (DNA) or 4 vector (rAd5) mix affects the immune response to that component**
- **However…..**

Peptide-specific Antibody Responses in Mice



Antibody Response Focuses on Peptide 27 When all Three Clades are Given

Env A27: TDIISLWDQSLKPCV
Env B27: HEDIISLWDQSLKPC
Env C27: EDIISLWDQSLKPCV

The clade-specific peptide responses are lost. This will make it very difficult to quantify a loss of immunogenicity of one of the envelope components within the 3 envelope mix in a potency assay.

For T cell Responses:

What we have so far:

PEPTIDE	Region	ALL	A only	B only	All but A	All but B	All but C
Best-clade specific	A	✓	✓			✓	✓
EnvA079	A	✓	✓			✓	✓
EnvA128	A	✓	✓			✓	✓
cross react	A	✓	✓	✓		✓	✓
Best-clade specific	B	✓		✓	✓		✓
EnvB017	B	✓		✓	✓		✓
cross react	B	✓	✓	✓	✓		✓
Best-clade specific	C	✓			✓	✓	
cross react	C	✓	✓	✓	✓	✓	

Conclusions

- **Immunologic potency testing of a multiclade HIV vaccine will be challenging**
- **The phenomenon of immunologic dominance within multiclade, multicomponent vaccines may impact the analysis of potency results**

Immunology Core Section
Dr. Robert Bailer

Back Row, Left to Right: Adrienne Campbell, Laurie Lamoreaux, Richard Koup, Ellen Turk, John Rathmann
Front Row, Left to Right: Robert Bailer, Mara Abashian, Jennifer Fischer